Journal of Thermal Analysis and Calorimetry, Vol. 64 (2001) 757–763

COMPARISON OF GENERIC HYDROCHLOROTHIAZIDE FORMULATIONS BY MEANS OF TG AND DSC COUPLED TO A PHOTOVISUAL SYSTEM

R. O. Macêdo, T. G. do Nascimento and J. W. E. Veras*

Laboratório de Tecnologia Farmacêutica, Universidade Federal da Paraíba, Campus I, João Pessoa, PB, 58059-900, Brazil

Abstract

The compatibilities and stabilities of some binary mixtures and generic hydrochlorothiazide formulations were studied by using TG, DSC and a DSC-photovisual system. The kinetic parameters were determined via the Arrhenius equations. Tablet B presented higher compatibility and thermal stability than those of tablets A and C. The photovisual system demonstrated that the decomposition of tablet A occurs before the melting point, due to the Maillard reaction between the hydrochlorothiazide and lactose present in the formulation. The behaviour and rate constants of binary mixtures suggest that lactose can be substituted for microcrystalline cellulose, MC(101), in tablet A. The DSC and TG data revealed different characteristics of compatibility and stability in generic formulations from different manufacturers.

Keywords: formulations, hydrochlorothiazide, thermal analysis

Introduction

The new methods for the development of pharmaceutical formulations require a previous knowledge of the physical-chemical properties of the drug and excipients, and analytical instrumentation with which results can be obtained rapidly and simply. The thermal characterization of excipients and formulations affords the first parameters in compatibility and stability studies.

Thermal analysis can be employed for the purity determination [1], compatibility and stability studies [2, 3] and polymorphism determination [4, 5] of pharmaceutical drugs, and for the characterization of excipients and pharmaceutical formulations.

The present work compares the compatibilities and stabilities of some generic hydrochlorothiazide formulations, using TG, DSC and DSC coupled to a photovisual system.

* Author for correspondence: E-mail: ruimacedo@ltf.ufpb.br

1418–2874/2001/ $ 5.00

Akadémiai Kiadó, Budapest
Kluwer Academic Publishers, Dordrecht

Experimental

The excipients and tablet A were donated by LTF-UFPB. These tablets contained the following ingredients: hydrochlorothiazide 22.73, starch 43.63, lactose 24.54, PVP 3.82, explocel 2.28, talc 2.00 and magnesium stearate 1.00%. Tablets B and C were obtained in the local drugstore, both without a described formula. The hydrochlorothiazide drug, binary mixtures and tablets A, B and C were sifted through a 100 mesh sieve, homogenized in a porcelain cup for 10 min and conditioned in an amber flask. The behaviour of the binary mixtures hydrochlorothiazide:lactose and hydrochlorothiazide:MC(101) were determined at proportions of 9:1, 8:2, 7:3, 6:4, 5:5, 4:6, 3:7, 2:8 and 1:9 (mass/mass). The medium values and standard deviations (*sd*) were determined from triplicates of DSC and TG curves.

Compatibility studies

The DSC apparatus was previously calibrated via the melting points of indium (156.6±0.2°C) and zinc (419.5±0.3°C) standards. The heat flow and enthalpy were calibrated via the heat of fusion of indium (28.58±0.30 J g^{-1}), under the same conditions as for the samples. The correction factors were calculated in accordance with the procedures and specifications of Shimadzu.

The compatibility studies were carried out by means of the DSC curves obtained with the Shimadzu model DSC-50 calorimeter, under a nitrogen atmosphere at a flow rate of 50.0 ml min^{-1}, at a heating rate of 10.0°C min^{-1}, up to 500.0°C. The sample mass was 2.00 mg. The sample and the reference were hermetically sealed in an aluminium pan.

The photovisual system consisted of an Olympus microscope coupled to a Sony model VCC-D520 camera, with Intel image capture software, model Intel Smart Video Record III.

Stability studies

The stability studies were performed via the TG curves, in a Shimadzu model TGA-50H thermobalance, at a heating rate of 10.0°C min^{-1}, under an air atmosphere at a flow rate of 20.0 ml min^{-1}, up to 900.0°C. The sample mass was 6.00–6.50 mg. The TGA-50H was calibrated with calcium oxalate monohydrate under the same conditions.

The TG isothermal curves were obtained at the plateau in the TG curve before the initial temperatures of thermal decomposition for the drug, hydrochlorothiazide:lactose, hydrochlorothiazide:MC(101) and tablets A, B and C. The samples were heated at a heating rate of 20.0°C min^{-1} up to the isothermal temperature, at which they were kept for 4 h [6]. The isothermal temperature interval was 170–300°C, depending on the product.

The reaction order (n) was determined by graphical analysis, and the rate constants (k) were calculated by using the Arrhenius equations. The kinetic parameters n and k for the hydrochlorothiazide drug, the binary mixtures and tablets A, B and C

were chosen from the statistical data relating to the correlation coefficient (r) and standard deviation (sd) [7].

Results and discussion

Compatibility studies

The hydrochlorothiazide has a melting point in the range 268–270°C [8, 9]. The drug presented a melting point at 270.8±0.1°C, with a heat of fusion of 17.7±0.2 kcal kg^{-1}. The corresponding values for tablet A were 215.6±0.4°C and 1.5±0.5 kcal kg^{-1}, for tablet B 266.3±0.2°C and 8.4±0.3 kcal kg^{-1}, and for tablet C 267.9±0.3°C and 4.2±0.5 kcal kg^{-1}. The phase transition values indicated lower heats of fusion for the hydrochlorothiazide formulations, and particularly tablet A.

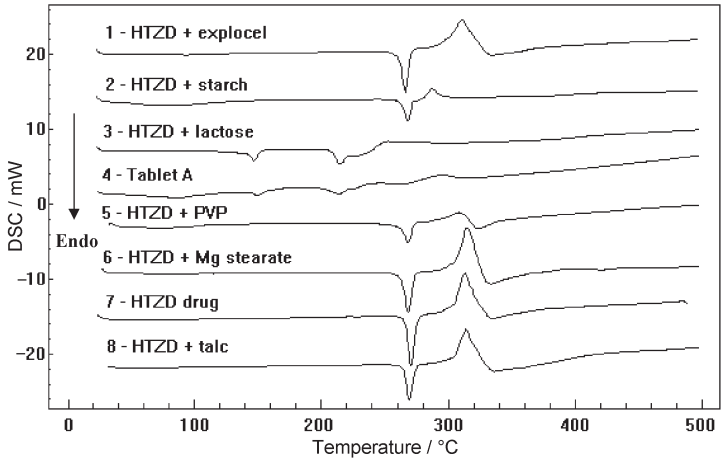

Fig. 1 DSC curves of hydrochlorothiazide (HTZD) binary mixtures

The DSC curves of the binary mixtures showed that lactose was the only excipient which reduced the melting point of the drug and decreased its heat of fusion, revealing a physical or chemical interaction between the drug and lactose (Fig. 1). This interaction was confirmed by study of the behaviour of binary mixtures in different proportions and by application of the photovisual system.

The behaviour of the binary mixtures of hydrochlorothiazide:lactose and hydrochlorothiazide:MC(101) in different proportions was examined. The DSC curves exhibited phase transitions with temperature displacements: for proportions of 9:1 253.1±0.1°C, for 8:2 248.2±0.2°C, for 7:3 242.5±0.5°C, for 6:4 235.5±0.4°C, for 5:5 226.2±0.3°C and for other proportions of hydrochlorothiazide:lactose 216.3±0.9°C and 271.4±0.7°C for all proportions of hydrochlorothiazide:MC(101). The DSC data revealed that lactose undergoes an interaction with hydrochlorothiazide. However, microcrystalline cellulose MC(101) did not display an interaction.

The DSC curve of the hydrochlorothiazide drug presented a melting point at 270°C; decomposition started at 306°C, with a change in colour. Lactose exhibited a phase transition, characteristic of a polymorphic excipient, at 218°C (Fig. 2F), with a

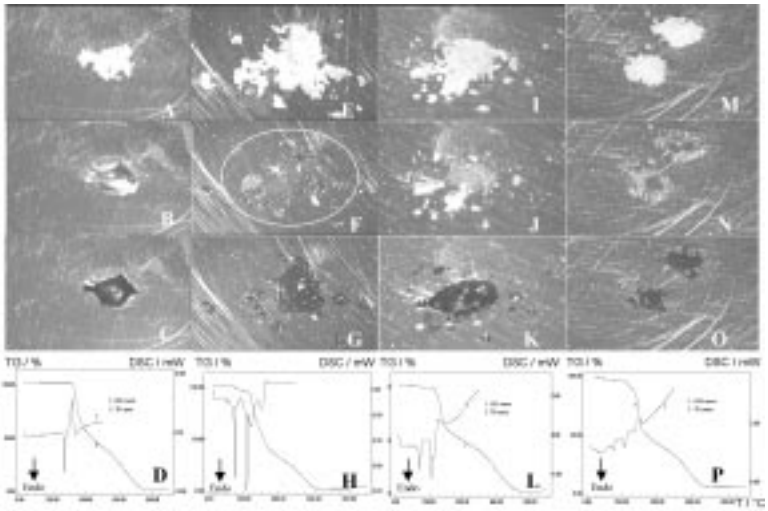

Fig. 2 DSC-photovisual pictures of hydrochlorothiazide (HTZD) drug: A (room temperature), B (270°C), C (306°C) and D (TG/DSC curves); lactose: E (room temperature), F (218°C), G (236°C) and H (TG/DSC curves); HTZD lactose: I (room temperature), J (214°C), K (225°C) and L (TG/DSC curves); tablet A: M (room temperature), N (207°C), O (220°C) and P (TG/DSC curves)

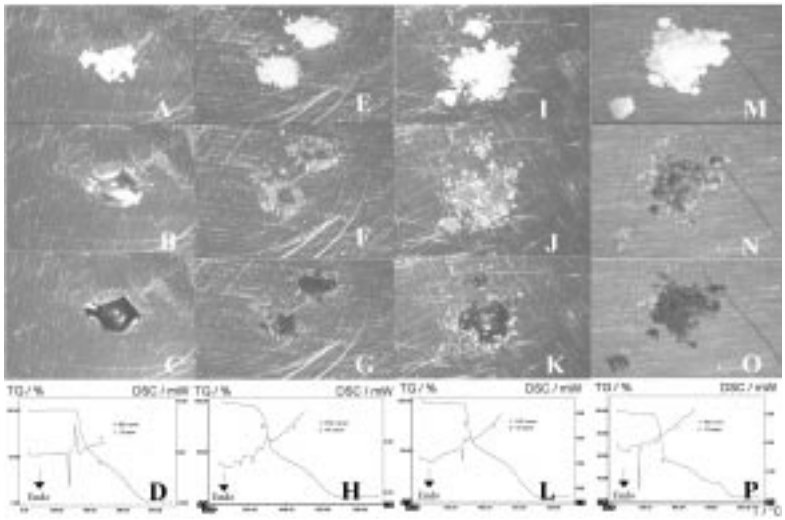

Fig. 3 DSC-photovisual pictures of hydrochlorothiazide (HTZD) drug: A (room temperature), B (270°C), C (306°C) and D (TG/DSC curves); tablet A: E (room temperature), F (207°C), G (220°C) and H (TG/DSC curves); tablet B: I (room temperature), J (270°C), K (275°C) and L (TG/DSC curves); tablet C: M (room temperature), N (165°C), O (267°C) and P (TG/DSC curves)

decreased melting point of 223°C according to the literature [10, 11] and its decomposition occurred at 236°C (Fig. 2G). The hydrochlorothiazide:lactose began a phase transition at 214°C, characterizing the melting point (Fig. 2J), followed by an intense brown colour at 225°C. The decomposition of the mixture started at 260°C (Fig. 2K) before the melting point of the drug.

Tablet A underwent a change in colour at 207°C (Fig. 3F) and total decomposition at 220°C (Fig. 3G), according to the TG profile. The photovisual images revealed the same process of decomposition as observed for hydrochlorothiazide:lactose, but with a difference of 5°C in decomposition temperature. Tablet B underwent a melting process at 270°C (Fig. 3J), with decomposition at 275°C (Fig. 3K), confirmed by the TG curve. Tablet C displayed a mass reduction at 165°C (Fig. 3N), corresponding to a phase transition in the DSC curve. The decomposition occurred concomitantly with the drug melting point at 267°C (Fig. 3O) and corresponded to the initial decomposition in the TG curve.

The DSC-photovisual system revealed that, before the melting point of the drug, the binary mixture hydrochlorothiazide:lactose and tablet A containing lactose undergo a Maillard reaction between the amine and carbonyl groups of hydrochlorothiazide and lactose, respectively, producing a brown colour [12] (Fig. 2K; Fig. 3G). This interaction was earlier demonstrated by LC-MS and ^{1}H NMR [13]. The photovisual system proved of great value in revealing chemical interactions that could not be detected by conventional DSC, in consequence of the predominance of physical interactions.

Stability studies

The TG data on the hydrochlorothiazide drug and tablets demonstrated thermal decomposition at the following temperatures: hydrochlorothiazide 313.6±0.2°C, tablet A 210.6±0.2°C, tablet B 265.8±0.1°C and tablet C 215.2±0.3°C. These results

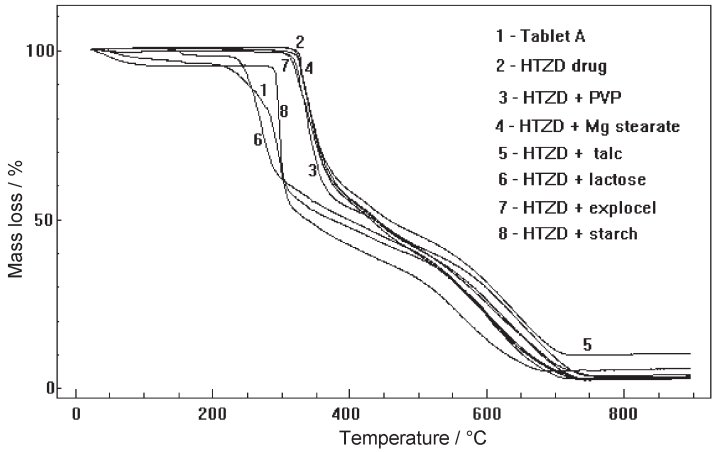

Fig. 4 TG curves of hydrochlorothiazide (HTZD) binary mixtures

provided evidence of the lower thermal stability of the tablets as compared with the hydrochlorothiazide drug.

The TG curves of the binary mixtures showed that the excipients lactose (236.7±0.4°C) and starch (300.4±0.3°C) were responsible for this reduction in the initial temperature of decomposition of tablet A (Fig. 4).

The TG-isothermal data allowed calculation of the kinetic parameters n and k, by using the Arrhenius equations for reactions of zero, first and second order. The statistical values at the studied temperatures, r=0.9997–0.9999 and sd=$1.0\cdot10^{-3}$–$1.5\cdot10^{-4}$, revealed that the best fits were obtained for the curves of mass *vs*. time for the hydrochlorothiazide drug, hydrochlorothiazide:MC(101) and tablets B and C, indicating reactions with zero-order kinetics. The TG-isothermal data on hydrochlorothiazide:lactose and tablet A demonstrated the best fits for the curves of 1/mass *vs*. time, indicating second-order kinetics.

The rate constants for hydrochlorothiazide:lactose and tablet A were similar, as were those for hydrochlorothiazide:MC(101) and hydrochlorothiazide drug. These data revealed that the drug and hydrochlorothiazide:MC(101) were more stable than tablet A and hydrochlorothiazide:lactose (Table 1).

Table 1 Rate constants of hydrochlorothiazide drug, hydrochlorothiazide:MC(101), hydrochlorothiazide:lactose and tablets A, B and C

Temp./ °C	Rate constants, k/s^{-1}					
	Drug	Drug: MC(101)	Drug: lactose	A	B	C
300	$3.93\cdot10^{-4}$(a)	–	–	–	–	–
290	$2.85\cdot10^{-4}$	–	–	–	–	–
280	$1.58\cdot10^{-4}$	–	–	–	$1.28\cdot10^{-3}$(i)	–
270	$9.20\cdot10^{-5}$	$1.17\cdot10^{-4}$	–	–	$7.04\cdot10^{-4}$	–
260	$4.43\cdot10^{-5}$	$4.54\cdot10^{-5}$	–	–	$3.27\cdot10^{-4}$	–
250	$1.94\cdot10^{-5}$(b)	$2.78\cdot10^{-5}$(c)	$5.78\cdot10^{-4}$(e)	$1.35\cdot10^{-4}$(g)	$6.83\cdot10^{-5}$(j)	–
240	–	$5.60\cdot10^{-6}$	$9.97\cdot10^{-5}$	$7.27\cdot10^{-5}$	$1.67\cdot10^{-5}$	–
230	–	–	$7.96\cdot10^{-5}$	$4.30\cdot10^{-5}$	–	–
220	–	$4.20\cdot10^{-6}$	$4.85\cdot10^{-5}$	$1.01\cdot10^{-5}$	–	$3.07\cdot10^{-4}$
210	–	$3.50\cdot10^{-6}$	$1.50\cdot10^{-5}$	$2.55\cdot10^{-6}$	–	$9.15\cdot10^{-5}$
200	–	$2.48\cdot10^{-6}$(d)	$8.23\cdot10^{-6}$(f)	$1.06\cdot10^{-6}$(h)	–	$3.20\cdot10^{-5}$(k)
190	–	–	–	–	–	$1.07\cdot10^{-5}$
180	–	–	–	–	–	$5.50\cdot10^{-6}$
170	–	–	–	–	–	$1.25\cdot10^{-6}$(l)

Standard deviation for (a, b) – drug: ±0.15 and ±0.12; (c, d) – drug:MC(101): ±0.18 and ±0.13; (e, f) – drug:lactose: ±0.17 and ±0.14; (g, h) – tablet A: ±0.15 and ±0.14; (i, j) – tablet B: ±0.16 and ±0.15; (k, l) – tablet C: ±0.17 and ±0.15

The rate constants showed the higher stability of the hydrochlorothiazide drug relative to those of the studied formulations. Tablet B displayed a higher stability than those of tablets A and C (Table 1).

The TG and kinetic data were of value for a thermal differentiation of the hydrochlorothiazide formulations, and suggested the substitution of lactose for MC(101) in tablet A, in consequence of its higher thermal stability.

Conclusions

The DSC-photovisual data revealed chemical interactions in the hydrochlorothiazide:lactose mixture and tablet A, leading to thermal decomposition with a change in colour. The behaviour of the binary mixtures indicated a physical interaction between hydrochlorothiazide and lactose, and high compatibility in the hydrochlorothiazide:MC(101) mixture.

The TG data indicated differences in stability between the studied tablets and showed that MC(101) can increase the drug stability in hydrochlorothiazide formulations. Tablet B exhibited a higher thermal stability than those of tablets A and C.

The thermal analysis demonstrated significant differences between the generic formulations from different manufacturers.

* * *

The authors thank to CNPq, CAPES and MS/ANVS for financial support.

References

1 R. O. Macêdo, T. G. Do Nascimento, C. S. F. S. Aragão and A. P. Barreto Gomes, J. Therm. Anal. Cal., 59 (2000) 657.
2 R. O. Macêdo, A. G. De Souza and A. M. C. Macêdo, J. Therm. Anal. Cal., 49 (1997) 937.
3 R. O. Macêdo, C. S. F. S. Aragão, T. G. do Nascimento and A. M. C. Macêdo, J. Therm. Anal. Cal., 56 (1999) 1323.
4 D. J. Giron and M. Drachi, J. Thermal Anal., 49 (1997) 913.
5 D. J. Giron, Pharm. Biomed. Anal., 4 (1986) 755.
6 C. J. Keattch and D. Dollimore, Introduction to Thermogravimetry, 2nd ed., Heyden 1975.
7 S.-Y. P. King, M. S. Kung and H. L. Fung, J. Pharm. Sciences, 73 (1994) 657.
8 The Merck Index, 12th ed., 1996.
9 United States Pharmacopeal, XXIII Ed., National Formulary, 18, 1995.
10 J. L. Ford and P. Timmins, Pharmaceutical Thermal Analysis: Techniques and Applications, Ellis Horwood, England 1989.
11 D. J. Giron, Thermochim. Acta, 248 (1995) 1.
12 D. D. Wirth and S. M. Gregg, J. Pharm. Sciences, 87 (1998) 31.
13 P. A. Harmon, W. Yin, W. E. Bowen, R. J. Tyrell and R. A. Reed, J. Pharm. Sciences, 89 (2000) 920.